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REMARKS

In the application, Claims 3 and 25-43 are pending and rejected. The Examiner states that the arguments filed December 27, 2004 have been considered but are not deemed persuasive. Applicants now submit amendments and additional remarks in support of patentability.

Claims 27 and 37 are rejected under 35 U.S.C. §112, 1st para., as containing subject matter not described in the specification. Specifically, the Examiner is of the opinion that the limitation that differential gene expression is diagnostic of a condition or disease is new matter.

The cited claims have been amended to add “profile” after “differential gene expression.” It is respectfully submitted that the limitation as now presented in the claims is fully supported in the specification and in the original claims. Original claim 15 introduced the limitation that “comparison of the test sample profile with the standard reference profile is diagnostic of a condition or disease.” Claims 27 and 37 differ only in that “comparison of the test sample profile with the standard reference profile” is replaced with “differential gene expression profile” Claim 27 depends from claim 26, which introduces the limitation that “one of the first and second sets of data corresponds to a reference sample and the other of the first and second sets of data corresponds to a test sample.” Claim 26 depends from claim 25, which includes the step of “comparing the first and second gene expression profiles to generate a differential gene expression profile”. The comments regarding claim 27 apply equally to claim 37 except that claim 37 depends from claim 36 which depends from claim 35.. Thus, it clearly follows from original claim 15 that because the first and second gene expression profiles are the profiles for the reference sample and the test sample, and comparison of the two profiles generates a differential gene expression profile, the differential gene expression profile is diagnostic of a condition or disease.

The Examiner has maintained the prior rejection that the written description does not provide enabling disclosure as required under 35 U.S.C. §112, 1st paragraph. Specifically, the Examiner asserts unpredictability as to what use that such displayed data is applied to.

It is respectfully submitted that the Examiner has misconstrued Applicant’s prior arguments, citing selected passages out of context in order to turn it around to support the

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rejection. Applicant's statements in the quoted paragraph on page 4 of the Office Action were directed to the value of providing a means for graphic visualization of data as compared to attempting to extract patterns from large volumes of numerical gene expression data. The underlined sentence, properly taken in the context of the preceding and following sentences is as follows:

One could look at *endless printouts of numerical gene expression data*, or enter the data into a computer classifier, to *attempt to identity patterns in the data based solely on numerical values*. This could take a long time and yield uncertain results, particularly when differential responses are observed. *On the other hand, or in combination with numerical analysis, one could put the data in a format that allows it to be visualized as an image, not mere numbers in a list, where patterns can often be more easily discerned.*

(emph. in Office Action; *emph. added*)

The Examiner reverts to citing the Stoeckert, Jr. et al. article ("Microarray databases: standards and ontologies", *Nature Genetics Supplement* 32:469, Dec. 2002) for the position that the use of gene expression data was yet to be realized.

Applicants again reiterate that reliance on the Stoeckert et al. article is inappropriate for this position. As the title states, this article is a review of activities directed to adoption of common standards and ontologies that will permit exchange of microarray-based experiment data among different research labs. This article expressly addresses *microarray databases* and cannot be read to mean that all gene expression data or the results of analysis of such data are by their nature unpredictable as to their application. The broad application of the authors' conclusions about microarray databases to gene expression data as a whole is inaccurate. The point the Stoeckert et al. make is that common standards should be instituted to permit sharing of microarray data to avoid inconsistencies across different data formats. At page 469, the authors write:

Systems are needed for the management and storage of microarray data and, within this context, standards and the use of ontologies are crucial to managing and sharing these data. In this review, we discuss some of the progress that has been made by the research community, spearheaded by the Microarray Gene Expression Data (MGED) Society (<http://www.mged.org>), in establishing common standards for describing microarray data, systems for data management and transfer, and public repositories for data storage and mining.

While use of different terminologies and annotations may have made interformat data sharing difficult, it does not prevent the use or analysis of all gene expression data, nor does it impair the application of the results of such analyses to a particular purpose.

The usefulness of microarray-based gene expression data was already established and widely documented at the time of the invention. For example, the Background of the Invention at page 5, line 17, cites Lockhart, et al., "Expression monitoring by hybridization of high-density oligonucleotide arrays", *Nature Biotechnology*, 14: 1675-1680 (1996). See also Bowtell, "Options available-from start to finish- for obtaining expression data by microarray", *Nature Genetics Supp.*, 21: 25-32 (Jan. 1999), which describes commercial microarrays, arrayers, scanners and software that were available from several different vendors at the time of the invention. A copy of this article is attached as Exhibit A. The Stoeckert et al. article was published from 4 to 6 years after these specific references. Furthermore, Stoeckert et al. were writing about an international organization (MGED) made up of biologists, computer scientists and data analysts who had already recognized the value and usefulness of microarray-based gene expression data and whose aims were to facilitate the sharing and evaluation of microarray data to "maximize the value of microarray data by permitting greater opportunities for sharing information". To suggest that in 2002 that Stoeckert et al. were describing microarray gene expression data as having a usefulness that was yet to be realized is contrary to the entire purpose of their article and the efforts of the MGED that they were reviewing.

The Examiner's requirement that the displayed data have a specified, predictable use, e.g., to diagnose a specific disease or condition, exceeds the scope of the claims and the requirements for patentability. The invention is drawn to a method for generating a graphic display of gene expression data. The Court of Appeals for the Federal Circuit has already opined that manipulation of data to generate a display qualifies as patentable subject matter. (See *In re Alappat*, 33 F.3d 1526, 31 USPQ2d 1545 (Fed. Cir. 1994) (*in banc*).) Using the data elements and steps called for in the claims of the present application, a graphical display will predictably be generated. That display is predictably useful for identifying patterns in the data. Accordingly, there is nothing unpredictable about the claimed invention.

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Quoting an excerpt from the Background of the Invention in the present application at page 5, line 31:

However, the very power of the gene expression profiling techniques poses a challenge to data handling methods and systems, to methods and systems for manipulating and analyzing the data, and to methods and systems for displaying the data so that it can be comprehended, studied and used. That is, the DNA sequences and gene monitoring techniques produce enormous amounts of data, so much so that new techniques are necessary for handling the data, for making it useful and for manipulating, analyzing and displaying it.

Thus is the goal of the invention.

Tools for generating graphical images for viewing gene expression data have been developed by others, including ArrayDB, a microarray laboratory information management system (LIMS), developed by the NIH. See Ermolaeva et al., “Data management and analysis for gene expression arrays”, *Nature Genetics Supp.*, 20: 19-23 (Sept. 1998), a copy of which is attached as Exhibit B. Ermolaeva et al. describe a component of ArrayDB called “ArrayViewer”, which generates a display including a histogram that is created using ratios of gene expression intensity values. Michaels, et al. (“Cluster analysis and data visualization of large-scale gene expression data”, *Pacific Symposium on Biocomputing* 3:42-53 (1998), copy attached as Exhibit C) describe a different approach to visualization of data to “reveal correlated patterns of gene expression from time series data.” This method represents genes as lines in an interconnected network. Eisen et al (“Cluster analysis and display of genome-wide expression patterns”, *Proc. Natl. Acad. Sci. USA* 95: 14863-14868, Dec. 1998, copy attached as Exhibit D) describe a statistical algorithm to arrange genes according to similarity in gene expression and generation of a graphic display that conveys “the clustering and the underlying expression data simultaneously in a form intuitive for biologists.” Based on these three examples, it is apparent that others of skill in the art were working contemporaneously with Applicants to devise methods for visualization of gene expression data that were useful for helping researchers recognize patterns in gene expression data. As stated by Michaels et al, “the coherence of these patterns suggests an order that conforms to a notion of shared pathways and control processes that can be experimentally verified.” Eisen et al. opine that what is needed is “a holistic approach to analysis of genomic data that focuses on illuminating order in the entire set of observations,

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allowing biologists to develop an integrated understanding of the process being studied.” Accordingly, the usefulness of visualized information such as that produced by the claimed invention was not only predictable at the time the application was filed, but readily apparent to, and sought by, others skilled in the art. Each described method provides means for looking at a set of gene expression data to identify patterns that would not be readily apparent from numerical data alone.

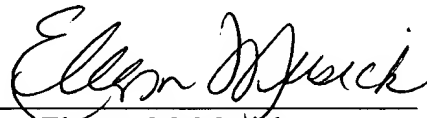
Section 112, 1st paragraph requires that the written description of the invention provide “full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same”. It is respectfully submitted that these requirements have been met, and that Applicants’ invention as disclosed and claimed has predictable usefulness that would be readily recognized by those of skill in the art.

In view of the foregoing remarks, Applicants submit that all bases for rejection have been addressed and overcome such that the claims as now presented are enabled and allowable over the prior art. Accordingly, Applicants respectfully request that the Examiner withdraw all outstanding rejections and issue a notice of allowance for all claims now in the application.

Respectfully submitted,

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By: _____



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